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SCIENCE

A Thrombin-Activated PAR-1 Pathway Drives Pancreatic Ductal Adenocarcinoma (PDAC) Growth and Metastasis

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Pancreatic ductal adenocarcinoma (PDAC) is a lethal cancer characterized by a wide range of mutations and a dense stromal environment that makes the disease resistant to chemotherapy. This chemoresistance, coupled with late stage detection, often leads to fatal prognoses for patients diagnosed with PDAC. Little progress has been made in improving patient outcomes over the past 40 years and there is a need for innovative approaches to characterize molecular pathways involved in PDAC development.

The purpose of this study is to define the role of a transmembrane receptor, PAR-1, in PDAC malignancy, to identify potential targets for therapeutic intervention. Previous studies have shown that the PAR-1 pathway is thrombin-activated, which provides a mechanism of experimental control over its activation. An assay to measure cell migration was used to quantify metastatic abilities of a representative PDAC cell line, KPC2, in the presence or absence of thrombin. The expected result was an increase in cell migration across the membrane following thrombin treatment, indicating increased metastatic ability. Initial results have confirmed this hypothesis and provided evidence that the PAR-1 pathway is critical for pancreatic tumor development and metastasis.

As this research progresses, further work will be done to characterize downstream factors under the control of PAR-1, which will contribute to the understanding of how this pathway induces tumor progression. Furthermore, PAR-1 is a major component of the thrombosis and coagulation pathways, and RNA sequencing data will be used to identify cell types and factors critical to PAR-1-dependent immune evasion.

Research advisor Stephen Konieczny writes: "Pancreatic ductal adenocarcinoma is a lethal cancer with no satisfactory therapeutic strategies available to patients. Emily's research has identified the thrombin-PAR-1 signaling pathway as critical to cell migration and cancer metastasis, providing important new insights in developing effective therapeutics that target this deadly disease."

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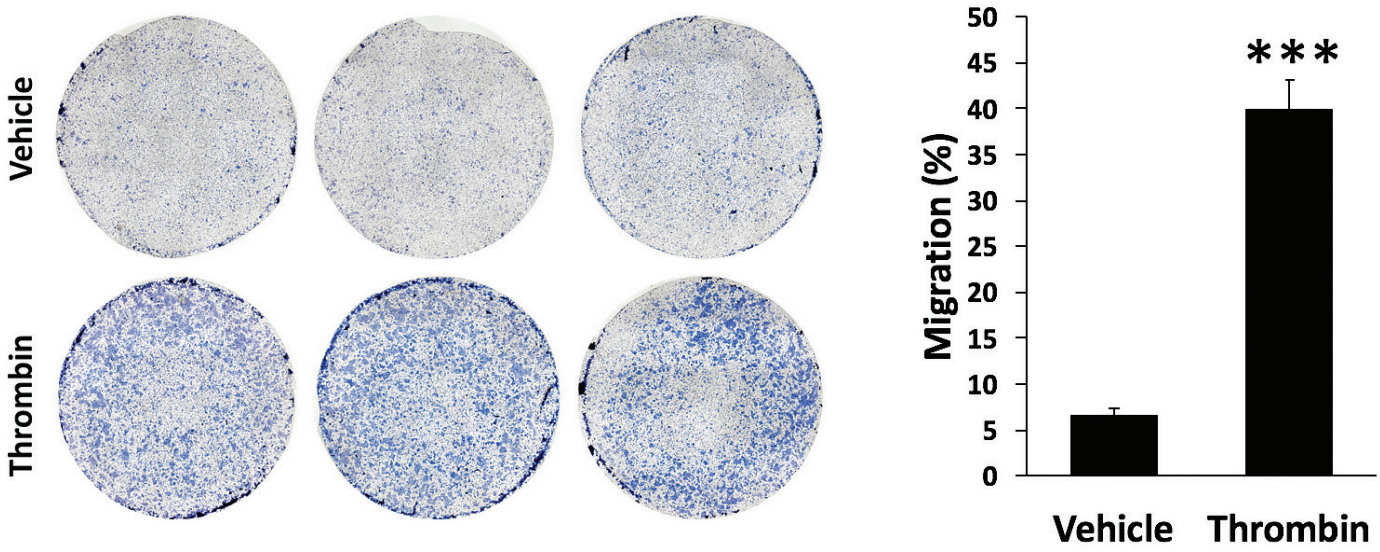

Results of the transwell migration assay measuring metastatic ability of a PDAC cell line. The thrombin treated cells show significantly increased migration (indicated by the darker stain) when compared to the vehicle treated cells, *** $p < 0.001$.

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